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Deep Brain Stimulation for Treatment-Resistant Schizophrenia: A Systematic Review

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Abstract

Background: Resistance to treatment characterizes a substantial portion of patients with schizophrenia. Without adequate symptom control from medication, these patients are left with few therapeutic options.

Objective: Given the recent success of Deep Brain Stimulation (DBS) in treatment-refractory neuropsychiatric disorders such as depression, obsessive-compulsive disorder, substance use disorder, and Tourette syndrome, we reviewed the existing evidence for DBS in schizophrenia.

Methods: We searched PubMed and MEDLINE for articles and conducted a systematic review on DBS as a treatment for schizophrenia in line with the PRISMA-P 2020 guidelines.

Results: After the search and screening process, we reviewed a total of three articles with eleven patients implanted. The nucleus accumbens (n = 3), subgenual anterior cingulate cortex (n = 4), habenula (n = 2), and substantia nigra pars reticulata (n = 1) were all targeted for stimulation. Stimulation resulted in symptom reduction on respective outcome measures in nine of ten patients stimulated (one patient was explanted without stimulation). There were ten adverse events across the eleven procedures and five of these were deemed serious adverse events, comparable to other reports of DBS. Three of these events occurred in the same patient, while one event coincided with a patient's discontinuation of their own antipsychotic regimen. None resulted in permanent harm.

Conclusion: Despite a limited experience, DBS is likely safe, and potentially effective in patients with refractory schizophrenia. Further investigation is necessary to establish ideal targets for stimulation.

Keywords: Deep brain stimulation (DBS); Schizophrenia; Nucleus accumbens; Substantia nigra

Introduction

Schizophrenia is a chronic, debilitating psychiatric disorder affecting over 20 million people worldwide [1]. The diagnosis of schizophrenia requires two or more of the following characteristics: 1) delusions, 2) hallucinations, 3) disorganized speech, 4) disorganized or catatonic behavior, and 5) negative symptoms such as flat affect or avolition, with at least one of the first three characteristics present [2]. Many patients typically exhibit considerable morbidity as their disease can cause cognitive impairment [3], strain interpersonal relationships [4], and is often associated with other psychiatric illnesses [5-8]. Additionally, the rates of all-cause mortality, natural-cause mortality, and suicide are higher in this population [9,10].

Historically, the proposed pathophysiology of schizophrenia has centered around disordered dopamine regulation [11-13]. More specifically, a hyperdopaminergic mesolimbic pathway and hypodopaminergic mesocortical pathway are thought to cause the positive and negative symptoms, respectively [14,15]. First-line treatment for schizophrenia is with antipsychotic medication, often taken chronically to prevent psychotic episodes [16]. The original antipsychotics (*typical* antipsychotics), are D_2 receptor antagonists and treat only the positive symptoms of schizophrenia. Second-generation antipsychotics, also known as *atypical*, generally demonstrate a decreased affinity for D_2 receptors while also affecting serotonergic, cholinergic, and adrenergic synapses [17]. However, pharmacologic treatment is not without its drawbacks as many antipsychotics display metabolic, cardiovascular, endocrine, and neurological side effects that can impact patient adherence or necessitate discontinuation of a medication that effectively treats their disease.

Approximately 10-30% of schizophrenic individuals are deemed treatment-resistant [18-20], meaning they failed two or more trials of an antipsychotic [21]. These patients are often started on clozapine, the most effective antipsychotic drug available. Clozapine is only indicated for refractory schizophrenia because it can cause agranulocytosis, a dangerously low level of white blood cells in the blood [22]. Even so, only about a third of patients will demonstrate a response to clozapine [23,24]. Those who do not respond adequately or cannot tolerate clozapine are then left with few alternatives. Because of the exorbitant societal burden that comes with both controlling patients' symptoms and managing the psychosocial factors influenced by their disease, there is a continued need to find better methods for controlling schizophrenia symptoms [25].

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Since many symptoms are associated with dysregulation of the dopamine system, potential treatments may include targeting of dopaminergic brain regions. Among the more intriguing, nonpharmacologic options for treatment-resistant schizophrenia are neuromodulatory methods such as Deep Brain Stimulation (DBS). Originally indicated for symptomatic improvement in movement disorders such as Parkinson's Disease and essential tremor, potential therapeutic applications of this technique have grown in recent years to include neuropsychiatric conditions like depression [26], Obsessive-Compulsive Disorder (OCD) [27], substance use disorder [28,29], and Tourette syndrome [30,31].

Aside from its success in other psychiatric disorders, DBS offers an opportunity to directly modulate aberrant circuits in schizophrenia. In animal models of Parkinson's disease, DBS prevented pathological oscillations associated with the disease and restored normal neuronal activity [32,33]. Multiple lines of evidence have demonstrated aberrant electroencephalographic (EEG) activity in schizophrenia patients across several frequency bands during both cognitive tasks and at rest [34-36]. The most frequently observed differences are in the gamma band, the dominant frequency for local, cortical network communication [37]. Interestingly, task-based studies revealed decreases in gamma power and synchronization in schizophrenia [34,38], whereas investigations of resting-state EEG found increased gamma power [39-41]. Thus, the utility of DBS may lie in its ability to interfere with this aberrant activity and restore more normal oscillatory patterns.

However, few studies have investigated DBS as a therapeutic option for schizophrenia. A single report from the 1950s described intense feelings of rage and fear during stimulation of the amygdala in a patient with schizophrenia [42], yet no further research had been published until the last few years. In this review, we examined the current literature on DBS as a treatment for refractory schizophrenia and emphasize the need for larger, randomized controlled trials to evaluate treatment efficacy. We also summarize existing information on potential targets and suggest the nucleus accumbens (NAc) and substantia nigra pars reticulata (SNr) as structures warranting further investigation.

Methods

Search Strategy

This study was performed according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses Protocols (PRISMA-P) 2020 statement standards [43]. Online databases, PubMed and MEDLINE, were searched for relevant studies in early November 2021 utilizing appropriate Boolean modifiers. Our exact search terms were *"Deep Brain Stimulation" OR "DBS" AND "Schizophrenia."* Two independent researchers screened and selected relevant articles based on title and abstract. Relevant articles were then screened for eligibility criteria. We also screened several reviews we encountered during our search, namely Mikell *et al.* [44], Mikell *et al.* [45], and Agarwal *et al.* [46].

Eligibility Criteria

We excluded articles on disorders other than schizophrenia, treatments other than DBS, non-human studies, and review articles. All remaining articles were peer-reviewed, original case reports, case series, or randomized trials written in English. No titles were excluded based on the date of publication.

Data Extraction

Two authors compiled a list of citations after screening the titles and abstracts. After discussing and agreeing on the eligibility criteria, the two authors independently reviewed the full-text articles that met the criteria. Information regarding the study design, participant characteristics, location of targets, duration of stimulation and follow-up, and outcome measures were extracted for comparison. Given the small number of patients across the eligible studies, we were unable to quantitatively assess the strength of evidence.

Three scales were used as primary endpoints for the studies included, namely the Positive and Negative Syndrome Scale (PANSS), Brief Psychiatric Rating Scale (BPRS), and Scale for the Assessment of Negative Symptoms (SANS). The PANSS is a 30-item scale consisting of positive symptoms, negative symptoms, and general psychopathology subscales. Each item is given a rating between one and seven, with higher scores representing more severe symptoms [47]. The BPRS evaluates up to 24 psychotic symptoms, each of which is scored from one to seven based on symptom severity [48]. Finally, the SANS measures negative symptoms on a 25-item scale scored from zero to five for each item [49].

Quality Assessment

Two authors independently assessed the risk of bias for the outcomes of each study in accordance with AHRQ guidelines [50].

Results

Study Selection

Our search of the literature in PubMed and MEDLINE yielded a total of 238 titles (120 and 118, respectively). We found no additional articles from other sources. After removing duplicates, 120 titles remained. Six articles were selected after screening based on their titles and abstracts. One case report [51] contained data from a patient that was also reported in a randomized trial [52], and therefore, was excluded. Another study [53] did not evaluate DBS as a treatment for schizophrenia. Finally, a third article [54] featured a patient with both OCD and schizophrenia, but investigated DBS in the context of their OCD symptoms. Thus, three articles met our eligibility criteria (Figure 1).

Study Design

Of the three articles that met our criteria, one was a randomized trial [52], one was a case report [55], and one was a case series [56]. Study characteristics are detailed in (Table 1). A total of 11 patients were implanted with electrodes across the three studies. However, one patient, planned for NAc DBS, was never stimulated due to complications from surgery (see Adverse Events). The objective of these three studies was to treat both positive and negative symptoms. Each intended to assess the effects of stimulation over different follow-up periods. Wang and colleagues planned to stimulate for 12 months, however, one of the two patients was only stimulated for 10 months [56]. The other two studies stimulated for a minimum of six months. The single case report includes six months of stimulation data [55], however, this patient is part of an ongoing clinical trial (NCT01725334) that intends to stimulate participants

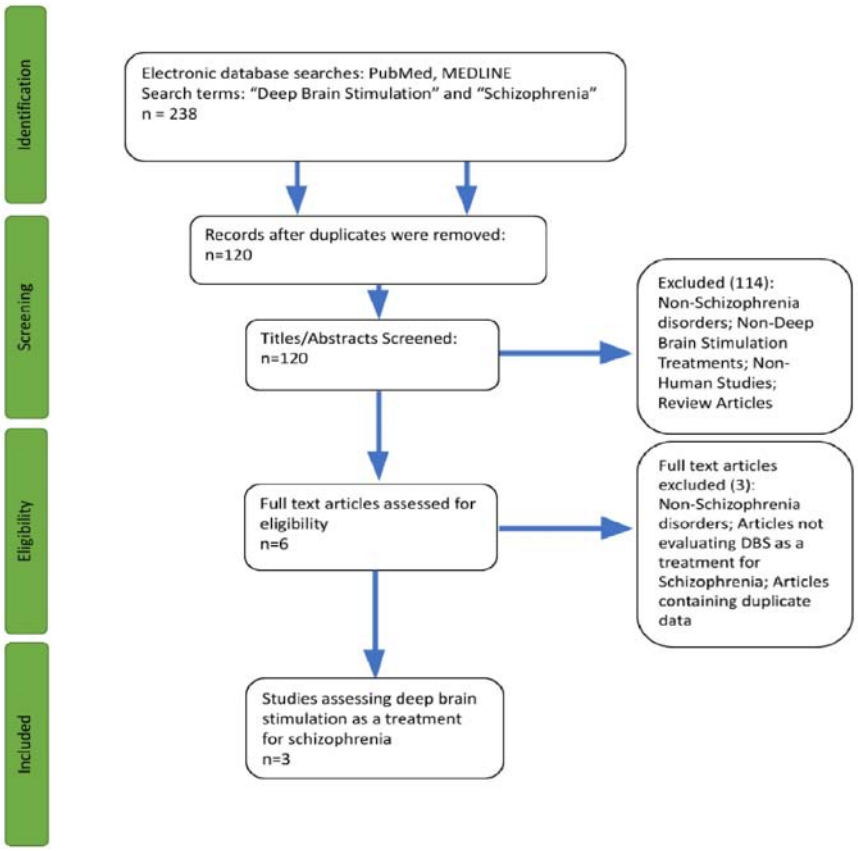

Figure 1: Schematic of literature search and screening process based on PRISMA-P 2020 guidelines [43].

Table 1: Characteristics of articles reviewed.

Article	*N*	Age range (% female)	Target(s)	Length of follow-up	Primary outcome measure(s)	Mean score improvement (%)
Corripio*et al*. [39]	7*	34-54 (57%)	Bilateral NAc (4*), Bilateral sgACC (4)	9-20 months	PANSS	30.8% (NAc), 23.5% (sgACC)
Wang *et al*. [43]	2	21, 26 (0%)	Bilateral Hb	12, 10 months	PANSS	11.1%
Cascella*et al*. [42]	1	35 (100%)	Bilateral SNr	6 months	BPRS, SANS†	52.4% (BPRS)

NAc = nucleus accumbens; sgACC = subgenual anterior cingulate cortex; Hb = habenula; SNr = substantia nigra pars reticulata; PANSS = Positive And Negative Syndrome Scale; BPRS = Brief Psychiatric Rating Scale; SANS = Scale for the Assessment of Negative Symptoms.
*One patient was implanted but did not undergo stimulation secondary to surgical complications.
†The full SANS score for this patient was not reported.

for a total of one year. For the randomized trial, patients received continued stimulation beyond 6-months until their disease was clinically stable. After stabilization, patients were eligible to enter a randomized, double-blind crossover phase if they demonstrated a ≥ 25% reduction in their PANSS that remained stable on 50% of the ensuing assessments. The crossover period consisted of two 12-week blocks, one with and one without stimulation, to which patients were randomized. Four patients met the criteria for the crossover phase, but one declined to participate [52].

Four different loci were stimulated among the ten patients studied; four in the subgenual anterior cingulate cortex (sgACC), three in the NAc, two in the Hb, and one in the SNr. Each of these sites has been implicated in the pathophysiology of schizophrenia (Figure 2). The sgACC is a component of the default mode network (DMN), which governs the resting state of the brain. Some studies have revealed decreased DMN deactivation during task-related experiments in patients with schizophrenia [57,58] (Figure 2A). However, there is continued debate over DMN pathology in schizophrenia [58]. There is more consensus about dopamine dysregulation in schizophrenia. According to one model, aberrant excitatory hippocampal input into the NAc releases the Ventral Tegmental Area (VTA) from ventral pallidal inhibition, resulting in an excess of dopamine release back onto the Nac [59-62] (Figure 2B). There are proposals to target several parts of this system [44]. It is also possible to target the dopamine system directly. The substantia nigra represents a very well-connected structure in the brain with roles in the dopamine system (pars compacta) as well as extensive projections to the thalamus (pars reticulata) [63]. In schizophrenia, cortical hypofunction leads to decreased striatal inhibition of the SN causing both increased dopamine release back onto the striatum as well as inhibition of the thalamus, further contributing to cortical hypofunction [63,64] (Figure 2C). Finally, the habenula's inhibitory inputs to both the SN

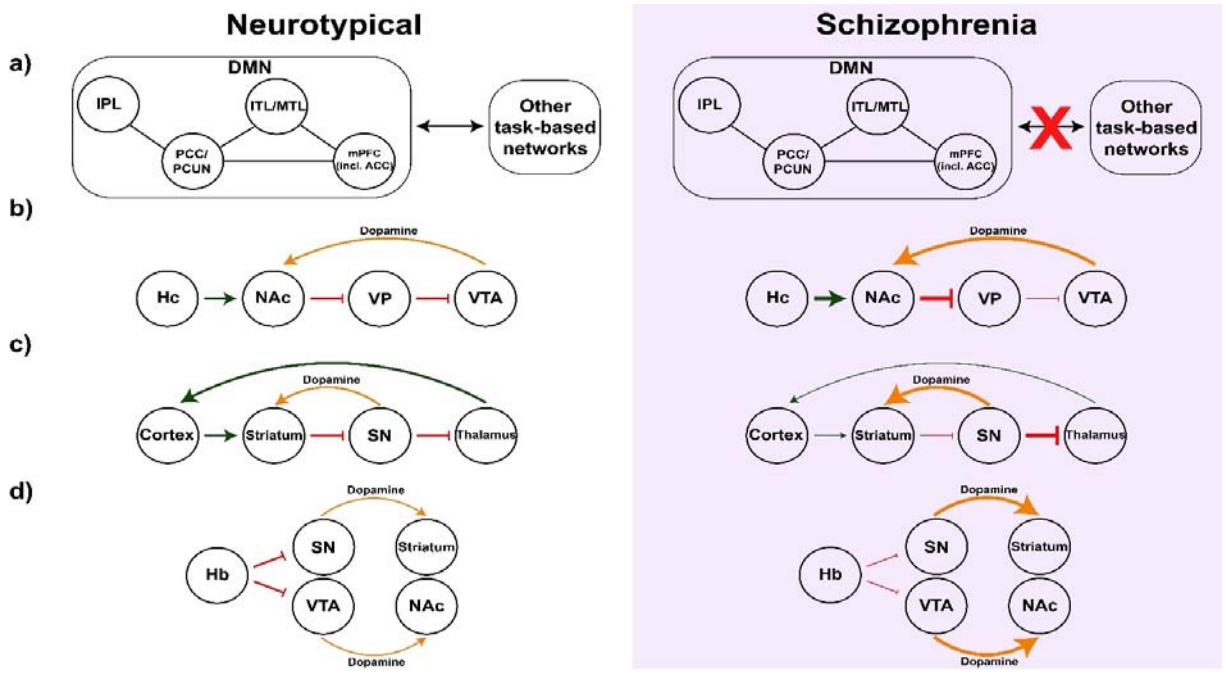

Figure 2: Circuit basis for each of the four DBS targets studied to date. Neurotypical circuits are shown in white and the changes with schizophrenia are shaded in purple. **a)** Attending to a task requires switching from the resting state network (DMN) to networks more suitable for goal-directed behavior. Some research shows that schizophrenia patients display less of this switching (red 'X'), even when faced with a task. Interrupting the DMN through sgACC-DBS may facilitate the activation of task-related networks. **b)** Hippocampal overactivity (bottom) increases NAc inhibition of the VP, thus increasing dopamine release from the VTA back onto the NAc. **c)** Decreased cortical excitation of the striatum (bottom) results in excessive SNc dopamine release as well as increased SNr inhibition of the thalamus, further decreasing cortical activity. **d)** Hb dysfunction (bottom) allows for unchecked dopamine release from the SNc and VTA. Key: green arrow – excitation; red bar – inhibition; black, single-headed arrow – dopamine; thick symbols – excess; thin symbols – deficient. Abbreviations: Sz (schizophrenia); DMN (default mode network); IPL (inferior parietal lobe); PCC (posterior cingulate cortex); PCUN (precuneus); ITL (inferior temporal lobe); MTL (mesial temporal lobe); mPFC (medial prefrontal cortex); sgACC (subgenual anterior cingulate cortex); Hc (hippocampus); NAc (nucleus accumbens); VP (ventral pallidum); VTA (ventral tegmental area); SNr/SNc (substantia nigra pars reticulata/compacta); Hb (habenula).

and VTA have led to questions regarding its role in schizophrenia, whereby habenular dysfunction begets excessive dopamine release from both of these structures [65,66] (Figure 2D).

Outcomes

Length of stimulation ranged from 6-20 months, with a mean of 11.9 ± 3.6 months. Across the ten patients, outcomes were largely positive (Table 1). Nine patients experienced improvement in their total respective outcome measures while one experienced a worsening of symptoms. This patient displayed improvements of 10.8% and 20.3% in their PANSS score at 6- and 7-month follow-up visits, respectively. However, at 10 months they were withdrawn from the study due to hospitalization for a psychotic episode. Their PANSS score had dropped 9.5% from the pre-stimulation baseline with a 69.2% increase in positive symptoms as well as a mild increase in negative symptoms (4.3%) [56].

Among the nine patients who demonstrated lower total outcome measures at the end of follow-up, there were a few who exhibited variable improvements in positive and negative symptoms. One patient implanted in the sgACC and one implanted in the NAc displayed increases in their negative PANSS scores [52]. The patient implanted in the SNr experienced a large reduction in their positive symptoms (Table 1), but only slight reductions in some of their negative symptoms. This patient was also found to have decreased performance (verbal and visuospatial learning/memory) on some aspects of cognitive testing and improved performance (verbal fluency) on others (55).

Only three (1 NAc, 2 sgACC) of the seven patients from the randomized trial entered the crossover phase, where patients received 12 weeks of stimulation followed by 12 weeks of no stimulation or vice versa. They were randomized such that one patient (NAc) began with 12 weeks of stimulation and the other two (sgACC) began with no stimulation. The two patients (sgACC) that entered the crossover phase in the *no stimulation* group both experienced worsening of symptoms when stimulation was turned off, and had to be withdrawn from the study before completing the crossover. The third patient, who began the crossover phase *with stimulation*, demonstrated a worsening of negative symptoms when stimulation was turned off, but still completed the trial. However, this change persisted, even after stimulation was turned back on. A fourth patient (NAc) also met symptomatic criteria for the crossover phase but declined to participate. Earlier in the study, it was discovered that this patient's stimulation had been accidentally turned off for several days and they had displayed a worsening of positive symptoms that improved when stimulation resumed. The four patients who had stimulation turned off all experienced a worsening of symptoms relative to when stimulation was on. This observation, together with the fact that nine of the ten patients across the three studies demonstrated an overall improvement during stimulation, suggest that DBS offers a promising therapeutic alternative in refractory schizophrenia patients

Table 2: Risk of bias assessment.

	Selection bias		Performance bias		Attrition bias	Detection bias			Reporting bias
Article	Randomization?	Accounted for confounding?	Accounted for concurrent intervention/ unintended exposure?	Fidelity to intervention protocol?	Missing data handled appropriately?	Interventions defined using reliable measures?	Outcomes defined using reliable measures?	Outcome assessors blinded?	Outcomes prespecified?
Corripio*et al*. [39]	Yes	No	No	Yes	No	Yes	Yes	No	Yes
Wang *et al*. [43]	N/A	No	No	Yes	No	Yes	Yes	No	No
Cascella*et al*. [42]	N/A	No	No	Yes	N/A	Yes	Yes	No	No

Table 3: Adverse events reported in each study.

		Transient AEs			Serious AEs	
Article	No. of procedures	Event	No. of events	Time to resolution	Event	No. of events
Corripio*et al*. [52]	8	Akathisia	1	Not specified	Perioperative internal capsule hemorrhage	1
		Positional dysesthesia	1	Not specified	Device infection	1
		Confusion	1	4 days	Seizures requiring AEDs	1
					Mood instability requiring hospitalization with occasional SI	1*
Wang *et al*. [56]	2				Aggravated psychotic episode requiring hospitalization	1
Cascella*et al*. [55]	1	Increased appetite causing significant weight gain	1	3 months		
		Decreased performance on tests of verbal and visuospatial learning/memory	1	>6 months†		

AE = adverse event; AED = antiepileptic drug; SI = suicidal ideation.

*This patient was hospitalized only once while having persistent mood instability. The number of episodes of SI was not specified. The authors note that this patient discontinued their antipsychotic medication immediately prior to displaying mood instability.

†This patient demonstrated decreased performance throughout the follow-up period but the authors remained uncertain as to whether this would continue.

Quality Assessment

Assessment of the risk of bias for each study is detailed in (Table 2).

Adverse Events

Adverse Events (AE) from the three studies are reported in (Table 3). In total, there were ten AEs across the eleven procedures. However, all ten AEs occurred in six patients. We classified five of the AEs as serious. All but one of the serious AEs (SAEs) occurred in the randomized trial [52], and three of them were in a single patient. This patient was planned for NAc DBS, but never received stimulation secondary to postoperative complications. They experienced a right internal capsule hemorrhage after surgery and subsequently developed an infection in the device, requiring complete hardware removal three months after surgery [52]. The patient did not suffer any permanent neurological deficits, however, they did have seizures that were controllable with antiepileptic medication. Another SAE,mood instability with occasional suicidal ideation, coincided with the patient's discontinuation of their own antipsychotic regimen despite previously demonstrating symptom reduction with a combination of antipsychotics and DBS [52].

Discussion

This review explores the current literature on DBS in patients with schizophrenia to evaluate its safety and efficacy as an alternative treatment for individuals whose symptoms cannot be controlled with antipsychotic medication alone. Little progress has been made in this area despite widespread use of DBS in the realm of movement disorders for decades [67,68]. Although research evaluating DBS in psychiatric disorders lagged behind considerably, there has been an explosion of studies investigating the technique in multiple illnesses including depression [26], Obsessive Compulsive Disorder (OCD) [27], substance use disorder [28,29], and Tourette syndrome [30,31]. Studies on DBS as a treatment for schizophrenia have only just recently begun to publish their data, with the three articles reviewed in this work all published within the last two years [52,55,56]. The most recent of these [55], is part of a clinical trial currently underway (NCT02361554). Additionally, another clinical trial (NCT01725334) began in 2012 to treat the negative symptoms of schizophrenia, targeting both the nucleus accumbens/ventral striatum as well as the VTA. This trial was unfortunately discontinued due to an inability to enroll participants. It is not clear why this group was unable to enroll any patients. One possible contributor is that they sought patients with predominantly negative symptoms, which might decrease their desire to participate in the study of an unproven therapy. Additionally, Corripio and colleagues report that the most common reason patients were excluded from their trial was because they did not believe they required treatment. The failure of the prior trial underscores another major challenge that accompanies enrolling schizophrenic patients in research. There are inherent ethical issues associated with consenting patients with psychosis, which is further muddied by neurosurgery's checkered past in treating psychiatric illnesses [69,70].

Despite existing hurdles and a lack of data, the early results are promising. Nine of the ten patients studied demonstrated sustained improvement in their respective outcome measures at the end of the follow-up period. The final patient had deteriorated at 10 months to where he was withdrawn from the study, but still displayed an improvement in symptoms at earlier time points [56]. The overall

safety of the procedure itself mirrored that of studies assessing DBS for other indications [71] and in all but one case, stimulation was associated with an improvement in psychotic symptoms.

Further studies are necessary to determine the ideal target for stimulation. However, given the heterogeneity of the disease, it is certainly possible that different structures may be suitable depending on symptomatology. From the available data, we believe the NAc to be the most encouraging. Patients showed greater improvement with NAc versus sgACC stimulation in a side-by-side comparison, albeit in a small sample [52]. This is consistent with the current views on the circuitry involved in the pathophysiology of the disease where overactivity of the hippocampus increases the inhibitory tone from the NAc to the ventral pallidum, thus removing inhibition on the VTA. The lack of VTA inhibition results in increased dopamine release back onto the NAc and the positive symptoms of the disease [59-62].

Although there is a report of exacerbating psychotic symptoms at higher amplitudes when NAc stimulation was used to treat severe depression [72], the three patients from the randomized trial did not display worsening of symptoms despite receiving higher stimulation parameters in the Nac [52]. This also corroborates evidence from an earlier report of NAc stimulation for treatment of OCD in an individual with a history of psychosis [54]. The stimulation amplitude was again higher than in Graa*et al.* [72] and the patient did not display a worsening of psychotic symptoms.

The SNr presents another intriguing target. With GABAergic projections to the mediodorsal nucleus of the thalamus (MD) and thus, widespread connections to the prefrontal cortex, it is hypothesized to play a role in the pathophysiology of schizophrenia [73-77]. Results from the one patient who underwent SNr implantation appear to support this hypothesis, however, a larger sample and longer follow-up is necessary to investigate the cognitive deficits that accompanied treatment in this patient [55]. More data should be available within the next few years as the patient participated in an ongoing clinical trial (NCT02361554).

Chief among limitations of our study is the scarcity of existing evidence, making the prospect of a meta-analysis futile. In line with this, seven out of the ten patients we report are from the same trial which undoubtedly introduces bias into our results. Our review demonstrates both the promise of DBS for yet another psychiatric indication and also emphasizes the need for larger, randomized trials in order to facilitate target-specific analyses. Importantly, the authors support the use of DBS in conjunction with antipsychotics and cognitive behavioral therapy as these remain the cornerstones of treatment. All patients reported in this study were maintained on an antipsychotic regimen during DBS treatment, and to the best of our knowledge, there are no reports of treatment with DBS alone for schizophrenia. Finally, we believe that future studies will reveal multiple reasonably safe and effective targets for patients with schizophrenia and location selection will focus on the individual symptoms and goals of treatment for each patient.

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Statement of Ethics

An ethics statement is not applicable because this study is based exclusively on published literature.

Conflict of Interest Statement

The authors do not report any conflicts of interest.

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Credit Author Statement

Jordan R. Saadon: Conceptualization, Investigation, Original draft writing, Review and editing, Visualization, Project administration. **Cassie Wang:** Investigation, Original draft writing, Review and editing, Visualization. **Bayan Razzaq:** Original draft writing, Review and editing. **Regina Leilani Kuhia:** Investigation, Original draft writing, Review and editing. **Nathaniel A. Cleri** Review and Editing. **Michael Egnor:** Review and editing, Supervision. **Sima Mofakham:** Conceptualization, Review and editing, Supervision, Project administration, Funding acquisition. **Charles B. Mikell:** Conceptualization, Review and editing, Supervision, Project administration, Funding acquisition.

Data Availability Statement

All data used in this study were obtained from previously published literature.

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